

Applicants: Jeremy Green et al.  
Application No.: 10/808,678

### REMARKS

#### The Claim Amendments

Claim 47 has been amended to define  $R^2$  as hydrogen, CN, -SR, -OR, -CO<sub>2</sub>R, -OC(O)R, -C(O)R, -C(O)N(R)<sub>2</sub>, -N(R)<sub>2</sub>, or -N(R)C(O)R. Support for this amendment is found in the claim as originally filed.

Claims 49 and 53 have been amended to recite specific chemotherapeutic or anti-proliferative agents. Support for these amendments is found in paragraph [00176] on page 59 of the specification.

Claim 50 has been amended to recite method of inhibiting c-Met kinase activity in a biological sample with a compound having formula I. Support for this amendment is found in claims 50 and 51 as originally filed.

Claims 51, 54, 56, and 69-70 have been canceled.

Claim 52 has been amended to recite a method of treating or lessening the severity of a disease or condition selected from gastric cancer, pancreatic cancer, ovarian cancer, breast cancer, or prostate cancer with a composition of the invention. Support for this amendment is found in original claims 54 and 56.

Claims 59, 60, 62, and 64 have been amended to define "x" as being an integer from 0-5. Support for this amendment is found in original claim 47, wherein Ar<sup>1</sup> and Cy<sup>1</sup> are each defined as being substituted with up to 5 occurrences of Z-R<sup>x</sup>. In addition, informalities in these claims and in claim 101 have been corrected by the use of commas and/or the conjunction "or."

Claim 68 has been amended to define  $R^2$  as hydrogen, -CN, -OR, -CO<sub>2</sub>R, -OC(O)R, -C(O)R, -C(O)N(R)<sub>2</sub>, -N(R)<sub>2</sub>, or -N(R)C(O)R. Support for this amendment is in the claim as originally filed.

None of the amendments contain new matter. Their entry is requested.

Applicants: Jeremy Green et al.  
Application No.: 10/808,678

### The Response

#### *Rejections under 35 U.S.C. § 112, first paragraph*

The Examiner has rejected claims 52-54 and 56 under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. In particular, the Examiner asserts that there is no reasonable correlation between the disclosed *in vitro* activity of the compounds of the invention and an *in vivo* activity. The Examiner also contends that it would not be predictable that the claimed methods would function as contemplated and that it would require undue experimentation by one of skill in the art to practice the invention.

Claims 53-54 and 56 have been canceled. Claim 52 has been amended to recite a method of treating or lessening the severity of a disease or condition selected from gastric cancer, pancreatic cancer, ovarian cancer, breast cancer, or prostate cancer. At the time of the invention, it was known that the hepatocyte growth factor receptor (HGF receptor, also known as c-Met) played a role in tumorigenesis. See, e.g., paragraphs [0048] to [0050] on pages 14-15 of the specification. The c-Met antagonist NK4, a protein fragment of HGF, was shown to have an inhibitory effect on the *in vivo* growth of human tumor cell lines derived from gastric cancer, pancreatic cancer, ovarian cancer, breast cancer, or prostate cancer in an immuno-compromised mouse model system. See the abstracts of Heideman et al., *J. Gene Medicine* 6: 317-327, 2004 (hereafter, “Heideman”); Tomioka et al., *Cancer Res.* 61: 7518-7524, 2001 (hereafter, “Tomioka”); Saga et al., *Gene Therapy* 8: 1450-1455, 2001 (hereafter, “Saga”); Martin et al., *Carcinogenesis* 24(8): 1317-1323, 2003 (hereafter, “Martin”); and Davies et al., *Int. J. Cancer* 106: 348-354, 2003 (hereafter, “Davies”). Furthermore, a selective small molecular inhibitor of c-Met was shown to have antitumor effects against a human gastric carcinoma cell line (GTL-16) in a mouse model. See page 7350 of Christensen et al., *Cancer Res.* 63: 7345-7355, 2003 (hereafter, “Christensen”). Taken together with the specification, Heideman, Tomioka, Saga, Martin, Davies, and Christensen clearly show that there is a reasonable correlation between the activation of c-Met in various cancers,

Applicants: Jeremy Green et al.  
Application No.: 10/808,678

the use of a c-Met inhibitor to inhibit cancer cell growth, and the use of the c-Met inhibitors of the invention to treat various cancers, as recited in claim 52.

For the therapeutic method discussed above, a skilled artisan would be able to discern an appropriate dosage and method of use based upon the information provided in the specification (see paragraphs [00142] to [00143] on pages 49-50) along with the general knowledge of one skilled in the art. Thus, the teachings of the specification, combined with the state of the art at the time of the invention, fully enable the claimed invention with respect to the aforementioned cancers and applicants respectfully request that the rejection of claim 52 under 35 U.S.C. § 112, first paragraph, be withdrawn.

The Examiner has rejected claims 49, 53, and 56 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. In particular, the Examiner asserts that a person skilled in the arts would not know what is meant by the term “chemotherapeutic or anti-proliferative agent.”

Claim 56 has been canceled. Claims 49 and 53 have been amended to recite compositions or methods wherein the additional therapeutic agents that are comprised by the compositions/methods are listed. Thus, the Examiner’s rejection has been obviated and applicants respectfully request that the rejection of claim 49 and 53 under 35 U.S.C. § 112, first paragraph, be withdrawn.

*Rejections under 35 U.S.C. § 112, second paragraph*

The Examiner has rejected claims 47, 49, 50, 53, 59-64, 100, and 101 under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the invention. In particular, the Examiner asserts that (i) when  $R^1$  is  $-(L)_mR$ , wherein  $m$  is 0 and  $R$  is  $C_{1-6}$  alkyl, it is unclear how this definition works when  $R$  is  $C_{2-6}$  alkyl; (ii) claims 49 and 53 employ the term “agent,” this making these claims ambiguous; (iii) claims 59-64 and 100 recite the variable “ $(ZR^X)_x$ , with the subscripted

Applicants: Jeremy Green et al.  
Application No.: 10/808,678

“x” not defined; and (iv) claim 101 does not employ commas or a correct Markush ending. Applicants traverse in part.

Regarding item (i), applicants argue that the definition of  $-(L)_mR$  is clear as recited in the instant claims. For example, when  $m$  is zero and  $R$  is an optionally substituted  $C_{1-6}$  aliphatic, the radical so defined can be any substituted or unsubstituted alkyl group having 1-6 carbons, including those having 2, 3, 4, 5, or 6 carbons.

Regarding item (ii), the instant claims have been amended to recite specific agents, thus obviating the Examiner’s rejections.

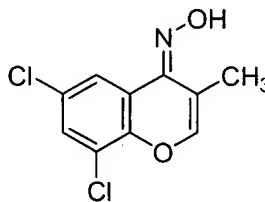
Regarding item (iii), the variable “ $(ZR^X)_x$ ” is not found in claims 61, 63, and 100. Claims 59, 60, 62, and 64 have been amended such that “ $x$ ” in these claims is 0-5, thus obviating the Examiner’s rejection.

Regarding item (iv), claim 101 has been amended to include commas and the conjunction “or” at the end of the claim, thus obviating the Examiner’s rejection.

Accordingly, applicants respectfully request that the Examiner withdraw the rejection of claims 47, 49, 50, 53, 59-64, 100, and 101 under 35 U.S.C. § 112, second paragraph.

*Rejections under 35 U.S.C. § 102(b)*

The Examiner has rejected claim 47 under 35 U.S.C. § 102(b) for allegedly being anticipated by U.S. Patent No. 4,065,574 (hereafter, “the ‘574 patent”). In particular, the Examiner asserts that the ‘574 patent teaches the following compound:



Applicants: Jeremy Green et al.  
Application No.: 10/808,678

R<sup>2</sup> cannot be alkyl in amended claim 47, thus obviating the Examiner's rejection. Accordingly, applicants respectfully request that the rejection of claim 47 under 35 U.S.C. § 102(b) be withdrawn.

#### Conclusion

Applicants request that the Examiner enter the above amendments and allow the claims to pass to issue. Should the Examiner deem expedient a telephone discussion to further the prosecution of the above application, applicants request that the undersigned be contacted at the Examiner's convenience.

Respectfully submitted,



---

Daniel A. Pearson (Reg. No. 58,053)  
Agent for Applicants  
Karen E. Brown (Reg. No. 43,866)  
Attorney for Applicants  
c/o Vertex Pharmaceuticals Incorporated  
130 Waverly Street  
Cambridge, MA 02139-4242  
Tel.: (617) 444-6790  
Fax.: (617) 444-6483